REMARKS

I. Interview of October 23, 2003

Applicant acknowledges with appreciation the courtesy shown in granting and conducting the personal interview between the undersigned attorney, Examiner Li and Examiner Wehbe.

II. Status of the Claims

Claims 1-31 have been cancelled, and new claims 32-49 have been added to address the Examiner's concerns from the interview about the claimed subject matter. As amended, the claims are drawn to the following aspects of the invention:

I. A method of inducing an immune response to a tumor in a subject, or protecting a subject from a cancer, which method comprises *in vivo* administration of total tumor cell RNA to epidermal cells of the subject. (Claims 32-36)

II. A method of inducing an immune response to a tumor in a subject, or protecting a subject from a cancer, which method comprises introducing epidermal cells contacted with tumor cell RNA *in vitro* to the subject. (Claims 37-42)

III. A method of inducing immune tolerance to an antigen in a subject comprising intravenous administration of antigen RNA is an amount effective to elicit immune tolerance against the antigen, wherein the antigen is an autoantigen, an allergen, or a transplant tissue antigen. (Claims 43-49)

Support for these claims can be found, for example, in the claims as originally filed, on page 13 line 23 to page 14 line 1 of the application, page 21, lines 6-25 of the application, and page 27, line 25 to page 28, line 25 of the application. No new matter has been added by these amendments.

III. Claim Objections

Claim 7 is objected to for depending from a cancelled claim. Claim 7 has been cancelled.

IV. Claim Rejections - 35 USC § 112, first paragraph

Claims 7, 11-12, 16-19, 21-23, and 31 stand rejected under 35 U.S.C. § 112, first paragraph for the reasons advanced in papers #5, 8, 17 and the instant Office Action. Generally, the Examiner contends that the specification does not provide an enabling disclosure consistent with the full breadth of the claims.

Applicant notes that claim 7 has been cancelled, and replaced with claims 34 and 40. Claims 34 and 40 now refer to an immune response that reduces or inhibits growth of a tumor (as opposed to inhibiting the growth of a pathogen). Applicants further note that claims 34 and 40 depend from claims 32 and 37. Claims 32 and 37 generally correspond to claim 5 and the rejection to claim 5 has been withdrawn by the Examiner. As the object of claims 34 and 40, i.e., reducing or inhibiting growth of a tumor, is achieved by the method of claims 32 and 37, applicant respectfully submits that claims 34 and 40 are also fully enabled and in compliance with 35 U.S.C. § 112, first paragraph.

Regarding claims 11-12, and 31, the Examiner states that these claims " encompass any route of administration using [RNA from] tumor cells from any source". These claims have been replaced with claims 35-36 and claims 41-42. Claims 35-36 and 41-42 specify that the total tumor cell RNA is taken from a tumor associated with the cancer, and that this RNA is administered to epidermal cells. Applicants respectfully submit that claims 35-36 and 41-42 comply with 35 U.S.C. § 112, first paragraph, and address the issues raised in this and past Office Actions.

Regarding claims 16-19 and 21-23 (which have been replaced by claims 43-49), the Examiner alleges that, example 4 nothwithstanding, "the specification fails to teach the real world utility for inducing tolerance for tumor and for pathogen cells". The Examiner questions the

circumstances that it is needed to induce tolerance to a tumor cell or a virus, and notes the problems associated with intravenous injection of, for example, the HIV virus.

Applicants note that new claims 43-49 relate to inducing immune tolerance to an antigen, wherein the antigen is an autoantigen, an allergen, or a transplant tissue antigen. As shown below, the person of ordinary skill in the art would readily recognize the utility in inducing tolerance towards autoantigens, allergens, and transplant tissues.

Example 4 details a subject undergoing a challenge by antigens, more particularly tumor associated antigens, which are analogous to the instantly claimed transplant tissue antigens. Recipient mice were intravenously administered 100 μg of total cellular RNA from the S1509a spindle cell tumor line, whereas control mice were intravenously administered saline. Both groups were then immunized by subcutaneously injecting disrupted S1509a cells three times at 6-7 day intervals. One week after the last injection, both groups were administered a source of tumor-associated antigens (TAA). As a measure of tolerance to the TAA, footpad swelling was measured. Recipient mice given the iv of the S1509a spindle cell tumor line demonstrated significantly smaller Delayed-type Hypersensitivity (DTH) compared to the control mice, indicating increased tolerance to TAA.

Further, the concept illustrated in Example 4 does have real-world utilty, as evidenced by the attached declaration of Dr. Richard Granstein under 37 CFR § 1.132 (Third Granstein Declaration). The Third Granstein Declaration demonstrates induced tolerance towards transplant cells, i.e., skin grafts, and accordingly transplant tissue antigens. Recipient mice were injected with total cellular RNA, and control mice were administered saline alone. Both groups were then given skin grafts under identical conditions. On average, 95% of skin graft area was tolerated in subjects that were intraveneously administered total cellular RNA, as compared to control subjects, in which almost half of the skin graft area exhibited necrosis. After two weeks, the percentage of graft necrosis in control mice was over 14 times the percentage of graft necrosis in the recipient mice. Applicants respectfully submit that the utility of claims 43-49 is demonstrated by this real-world application of the principal set forth in Example 4 of the specification.

The Examiner contends "that it is not appropriate to use the response to tumor cells' [RNA] as the sole support for microbial, allergen, autoantigen, or transplantation antigen[s]". Dr. Granstein's attached declaration details experiments performed in accordance with claim 43 of the present invention. These experiments demonstrate induction of tolerance to antigens, in this case, transplantation tissue antigens. Particularly, these experiments confirm the dramatically increased tolerance to skin grafts effected by intravenous administration of total cellular RNA. Thus Applicants have further supported the results of Example 4, and have supplied a real-world application of the principal exemplified therein.

The Examiner further contends that "simply administering an autoantigen as an attempt to reestablish the feature of self-tolerance is unlikely to be successful." The Examiner does not provide a specific basis for this personal opinion, instead relying on DNA vaccine references that purportedly demonstrate the distinctiveness of host responses to different types of antigens. Such reliance on unsubstantiated supposition does not establish a basis for rejecting the claims, which are based on the disclosed and exemplified discovery that intravenous administration of RNA induces a tolerization reaction to the molecules encoded by the RNA. The RNA can be for a single antigen or total cellular RNA.

The Examiner's opinion, and the purported results of the DNA investigations, runs counter to evidence regarding antigen RNA administration. Applicant has shown that intravenous administration of antigen RNA (not antigen DNA) is "effective" to induce tolerance to tumor cell antigens (as shown in Example 4) and is also effective in inducing tolerance to transplant tissue antigens (as shown in the attached Declaration). The law on this point is instructive:

> "The Examiner should **never** make the determination [of enablement] based on personal opinion. The determination should always be based on all the evidence" (MPEP § 2164.05 (emphasis in original)).

Here, Applicant respectfully submits that upon consideration of *all* the evidence, particularly the most-relevant evidence relating to intravenous administration of antigen RNA, a person of ordinary

skill would be enabled to intraveneously administer antigen RNA to ellicit tolerance to autoantigens, allergans, or transplant tissue antigens.

The Examiner next contends that the specification does not teach that using any total cell RNA could induce therapeutic tolerance to any autoantigen, any allergen, or any transplantation antigens. Applicant submits that the specification teaches that use of a total cell RNA would induce tolerance to autoantigens, allergens, and transplantation tissue antigens given that the total cell RNA contains the RNA of the particular antigen being tolerated. As explained on page 10, lines 13-15 of the application, use of total cellular RNA obviates the need to know the precise antigen or antigens that are relevant for induction of tolerance. The total cellular RNA must only include RNA of the tolerated antigen. Furthermore, this discovery concerns the route of administration (intravenous).

Such teaching is consistent with the breadth of the claims, as independent claim 43 recites administering antigen RNA . . . wherein the antigen is a autoantigen, allergen, or a transplant tissue antigen. Claim 44 further specifies that the antigen RNA is total cellular RNA from the tissue containing the antigen. Such RNA contains RNA of the tolerated antigen. Applicant submits that these claims are consistent with, and enabled by, the specification.

V. Claim Rejections - 35 USC § 112, second paragraph

Claims 2, 4, and 5 are rejected under 35 U.S.C. § 112, second paragraph for lacking proper antecedent basis. Claims 2, 4 and 5 have been cancelled. Applicant respectfully submits that the new claims provide proper antecedent basis, including proper reference to total tumor cell RNA.

VI. Claim Rejections - 35 USC § 103(a)

Claims 2, 3, 5, 7, and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ashley et al. (J Exp. Med., 1997, 186:1177-1182), in view of Beissert et al. (J. Immunol., 1995, 154:1280-1286). Ashley teaches a method for treating brain tumors comprising pulsing bone-marrow derived dendritic cells with RNA. Beissert teaches that Langerhans cells are immature dendritic antigen-presenting cells (APC) that are instrumental in tumor immunity. Applicant

respectfully submits that there is no motivation for substituting the bone marrow derived dendritic cells of Ashley with the Langerhans cells of Beissert, but even if there were, the combination does not teach administration to epidermal cells.

The Examiner admits that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so." The Examiner, while correctly stating the applicable rule, fails to provide such teaching, suggestion, or motivation to combine the references. In the previous Office Action (paper no. 17), the Examiner asserted that the skilled artisan would have been motivated to modify the teachings of Ashley in view of the critical role of epidermal cells in anti-tumor immunity purportedly taught in Beissert. Aside from the fact that Ashley teaches the critical role of mature dendritic cells (Langerhans cells are immature dendritic cells), Beissert explains that the brain is a unique site where tumors do not respond to immunotherapy protocols that are usually effective (page 1177, left side). Thus, considering Beissert as whole, one would not be motivated to focus on Langerhans cells, which the Examiner asserts are only generally associated with anti-tumor immunity, not brain tumors. Applicants respectfully submit that the Examiner has not established a motivation to combine the references, and that a prima facie case of obviousness has not been established.

Furthermore, even if the references were combined, there would not be a reasonable expectation of success. Ashley exclusively teaches use of RNA in mature dendritic cells that were isolated. Beissert teaches the criticality of inducing maturation of Langerhans cells, which are immature dendritic cells, with GM-CSF factor. A person of ordinary skill in the art would not be reasonable assured that Ashley's teachings would apply to Beissert's Langerhans cells.

Claims 2, 3, 5, 7, and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. Nos. 5,853,719 and 6,306,388 (collectively "Nair"), in view of Beissert. Initially, Applicant notes that Nair does not teach *in vivo* administration of RNA derived from tumors, as recited in newly submitted claims 32-36. Further, an epidermal APC is not disclosed in either Nair or Beissert. Although the Examiner adheres to the position that the immature dendritic cells of

Beissert are technically epidermal cells, a person of ordinary skill would not be motivated to administer total tumor cell RNA to epidermal cells (*in vivo or ex vivo*) based on the references themselves, and the accepted distinction between dendritic cells and epidermal cells.

Claim 6 stands rejected as being unpatentable over Nair in view of Beissert and U.S. Pat No. 6,403,080 issued to Segal. Segal teaches that opsonin-enhanced cells can be used as a vaccine for fibrosarcoma, and thus it would be obvious to select fibrosarcoma as an antigen of interest in connection with a vaccine, as taught by Nair and Beissert. Neither Nair nor Beissert, however, teach using epidermal cells as the APC. Segal does not supply this missing teaching.

V. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

By_____

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